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RESEARCH ARTICLE

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Safety and immunogenicity of quadrivalent meningococcal polysaccharide vaccine (MPV ACYW135) compared with quadrivalent meningococcal conjugate vaccine (Menactra®) in Malian children

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ABSTRACT

Affordable, polyvalent meningococcal vaccines are needed for use in emergency reactive immunization campaigns. A phase IV randomized, observer-blind, controlled study compared the safety and immunogenicity of a quadrivalent meningococcal polysaccharide vaccine (MPV-4, MPV ACYW135) and quadrivalent meningococcal ACWY conjugate vaccine (MCV-4, Menactra®). Healthy, 2- to 10-year-old children in Bamako, Mali, were randomized 1:1 to receive one dose of MPV-4 or MCV-4. Safety outcomes were evaluated for 6 months post-immunization. Immunogenicity for all serogroups was assessed for non-inferiority between MPV-4 and MCV-4 30 days post immunization by serum bactericidal antibody assay using baby rabbit complement (rSBA). From December 2020 to July 2021, 260 healthy subjects were consented and randomized. At Day 30 post-immunization, the proportions of subjects with rSBA titers ≥ 128 for all serogroups in the MPV-4 group were non-inferior to those in MCV-4 group. The proportions of subjects with rSBA ≥ 4-fold increase and rSBA titers ≥ 8 for all serogroups were similar among vaccine groups ($P > .05$). Geometric Mean Titers and Geometric Mean Fold Increases for all serogroups in both vaccine groups were similar ($P > .05$). Few local and systemic post-immunization reactions of similar severity and duration were observed within 7 days and were similar in both groups ($P > .05$). All resolved without sequelae. Unsolicited adverse events were similar in both groups regarding relationship to study vaccine, severity and duration. No serious adverse events were reported during the study period. MPV ACYW135 showed a non-inferior immunogenicity profile and a comparable reactogenicity profile to MCV-4 in Malian children aged 2–10 years.

Clinical Trial Registration: NCT04450498.

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Introduction

Neisseria meningitidis causes significant morbidity and mortality in children and young adults worldwide. Among 12 meningococcal serogroups identified so far, the majority of meningococcal disease is caused by six serogroups namely A, B, C, X, Y and W.[1] Until recently serogroup A was the main cause of major meningitis epidemics in the so-called "meningitis belt" in Sub-Saharan Africa, an area that stretches from Senegal in the West to Ethiopia in the East. The introduction of the conjugate meningococcal serogroup A vaccine (MenAfriVac®) through mass vaccination campaigns started at the end of 2010 leading to the virtual disappearance of meningitis due to serogroup A.[2] Since 2015, MenAfriVac® has been part of the infant Expanded Programme on Immunization (EPI) as a single dose at 9 months of age in the meningitis belt countries.[2] However, large outbreaks due to other serogroups of *N. meningitidis* are periodically occurring in Sub-Saharan Africa with substantial morbidity and mortality. Since 2013, *N. meningitidis* serogroup C has caused outbreaks in Nigeria and Niger, that has extended in 2017 to Burkina Faso, Mali and Benin.[3,4] In 2016 serogroup W caused large outbreaks in Togo and Ghana, and in around 2018, serogroup W accounted for around one thirds of the meningococcal diseases (MD) found in the meningitis belt.[5] In 2019 the predominant serogroup was C with 30% of isolates followed by X and W at 11% and 10%, respectively.[6–8] As affordable conjugated polyvalent vaccines are not yet available for use in this setting, several reactive vaccination campaigns with ACW or ACWY polysaccharide vaccines have been conducted to control the spread of the outbreaks.[7,9]

As recommended by WHO, the availability of significant quantities of vaccines will allow a constant supply of meningococcal vaccine containing *N. meningitidis* C and W polysaccharides for emergency stockpile to be used in reactive vaccination campaigns to control large outbreaks in African meningitis belt countries, or whenever needed.[7,8,10]

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A ACYW Meningococcal Polysaccharide Vaccine (MPV ACYW135) has been developed and licensed and has been widely used in China since 2012. The present study was performed to compare safety and immunogenicity of MPV ACYW135 (Group ACYW135 Meningococcal Polysaccharide Vaccine, Yuxi Walvax Biotechnology Co., Ltd., Yuxi, Yunnan, China) to Menactra® (Meningococcal [Groups A, C, Y and W-135] Polysaccharide Diphtheria Toxoid Conjugate Vaccine, Sanofi Pasteur Inc., Swiftwater, PA, USA) in 2–10 year old children in Mali, a country within the meningitis belt.

Methods

Participants and recruitment

The study, a Phase IV clinical trial, was designed as a randomized, observer-blind, controlled study and was conducted at the Centre pour le Développement des Vaccins du Mali (CVD-Mali), in Bamako, Mali. A total of 260 healthy children aged from 2 to 10 years with residence in the study area, who were fully vaccinated according to the local EPI schedule, and whose parents or legal guardians were capable and willing to bring their child to the site or to receive home visits for their child for all follow-up visits, were enrolled and managed by investigators at CVD-Mali in the study.

Ethics

This study was approved by the Ethics Committee of the Faculty of Medicine, Pharmacy and Odontostomatology) (FMPOS)/ University of Sciences, Techniques and Technologies of Bamako (USTTB), and the Institutional Review Board (IRB) of University of Maryland, Baltimore (UMB). The study was conducted according to *Good Clinical Practice* (ICH guidelines), the *Declaration of Helsinki*, and applicable local laws and regulations. Investigators informed the subjects' parents or legal guardians of all aspects pertaining to the subjects' participation in the study. Before any study procedure was initiated, parents or legal guardians provided written informed consent for the subject to participate into the study. The study was registered in clinicaltrials.gov as NCT04450498.

Vaccines and vaccine assignment

MPV ACYW135 vaccine is presented in two vials one containing the lyophilized formulation to be reconstituted before injection with the other vial containing the diluent. After reconstitution with diluent (sterile water), each dose of 0.5 mL contains 50 µg of each *N. meningitidis* group A, C, W, and Y purified polysaccharide. Menactra® vaccine is presented as full liquid single dose vial of 0.5 mL. Each dose contains 4 µg of each *N. meningitidis* group A, C, W, and Y conjugated to diphtheria toxoid.

Eligible subjects were randomized 1:1 to receive one single intramuscular injection of either MPV ACYW135 vaccine or Menactra®. A randomization list containing subject numbers and vaccine group assignments was generated according to blocking scheme (1:1) by an independent statistician using SAS 9.4. The study was designed and carried out in an observer-blind fashion. At the study site, the investigator had designated the blind and unblind teams in order to comply with the observer-blind design. Personnel was not allowed to change of team during study period. The unblind team was responsible for handling the randomization list and subjects' randomization, for vaccine preparation and administration, for vaccine accountability and storage. The site blind team was responsible for consenting, screening, enrolling and collecting the safety outcomes. The observer-blind design was maintained throughout the study period by the strict compliance to roles and responsibility of both blind and blind team as included in study site SOPs (Standard Operating Procedures). Additionally, periodical monitoring of study site by independent blind and unblind study monitors ensured the compliance to observer-blind procedures.

Safety assessment

After vaccination, subjects were observed for 30 minutes for any immediate post-immunization reactions. Solicited local and systemic reactions within 6 days after vaccination were collected by investigators through home visits or during on-site visits, which included: injection site induration and injection site pain, irritability, loss of appetite, drowsiness, vomiting and fever. Subject's parents were asked to report any adverse events whether or not he/she believed to be related to study vaccines for six months after vaccination. Thirty days after vaccination all subjects had a medical check and safety data were recorded as well as a blood draw for immunogenicity evaluation. Solicited reactions within 4 days were presumed to be vaccine-related. Assessment of causality in the case of unsolicited adverse events was performed by the study investigators.

Immunogenicity assessment

Primary and secondary immunogenicity endpoints were assessed at 30 days post vaccination. Blood samples were taken on the day of vaccination and 30 days after vaccination. Samples were tested by serum bactericidal antibody (SBA) assay using baby rabbit complement (rSBA) to A, C, Y, W meningococcal strains by the Vaccine Evaluation Unit, UK Health Security Agency, Manchester, UK. The primary immunogenicity endpoint was evaluated by the seroconversion rates as defined by the percentages of subjects with rSBA titers ≥ 128 to each of the four serogroups A, C, Y, W of *N. meningitidis* at Day 30 after vaccination along with its two-sided 95% CI, in accordance with WHO TRS 963 Annex 3 *Recommendations for Clinical Evaluation of Meningococcal C Vaccines*.[11] Secondary immunogenicity analysis included the proportions of subjects with a rSBA ≥ 4-fold increase 30 days after vaccination as compared to baseline unadjusted titers for all serogroups, proportions of subjects with rSBA titer ≥ 8 at 30 days after vaccination, as well as rSBA geometric mean titers (GMTs) of specific antibodies to groups A, C, Y, and W meningococci in both vaccine groups.

Statistical analyses

The primary hypothesis was that the seroconversion rate (percentages of subjects with rSBA titers ≥ 128 to each of the four serogroups 30 days after vaccination) in the MPV ACYW135

group was non-inferior to that in Menactra® group. The sample size was calculated based on non-inferiority test with alpha level of 0.025 and 80% power, assuming that seroconversion rate in the control group was 95% with non-inferiority margin at 10%. The sample size required for the study was 124 subjects per arm. After adjusting for 5% drop-out, 130 subjects per arm were due to be enrolled. Subjects' demographic characteristics, percentages with AEs and seroconversion rates in the two vaccine groups were compared using chi-square test for categorical variables or Student's *t*-test for continuous variable. Pre- and post-vaccination GMTs and their 95% confidence intervals (CIs) were calculated for each vaccine group and then compared between vaccine groups using Student's *t*-test. The ITT (Intention-to-treat) population included all subjects who had received the vaccination; PP (Per-protocol) population included all subjects who had received the vaccination and had the immunogenicity test at baseline and 30 days after vaccination.

Results

From December 23, 2020, to January 28, 2021, a total of 262 subjects aged between 2 and 10 years were screened, among whom 260 were enrolled and vaccinated. Two subjects were excluded at screening: one had a history of allergic reactions to EPI vaccines; the other had a chronic disease and was judged by the investigator not in good health. All 260 enrolled subjects were included in the safety analysis. Three subjects, one in the Menactra® group and two in the MPV ACYW135 group, were excluded from the immunogenicity analysis as they had traveled outside the study area and were not available for the blood draw at 30 days after vaccination. One further in the Menactra® group was not tested for serogroup Y rSBA as the serum volume was insufficient. Please see Figure 1 for the overall disposition of subjects.

No significant difference ($P > .05$) was observed between vaccine groups in baseline demographic characteristics of

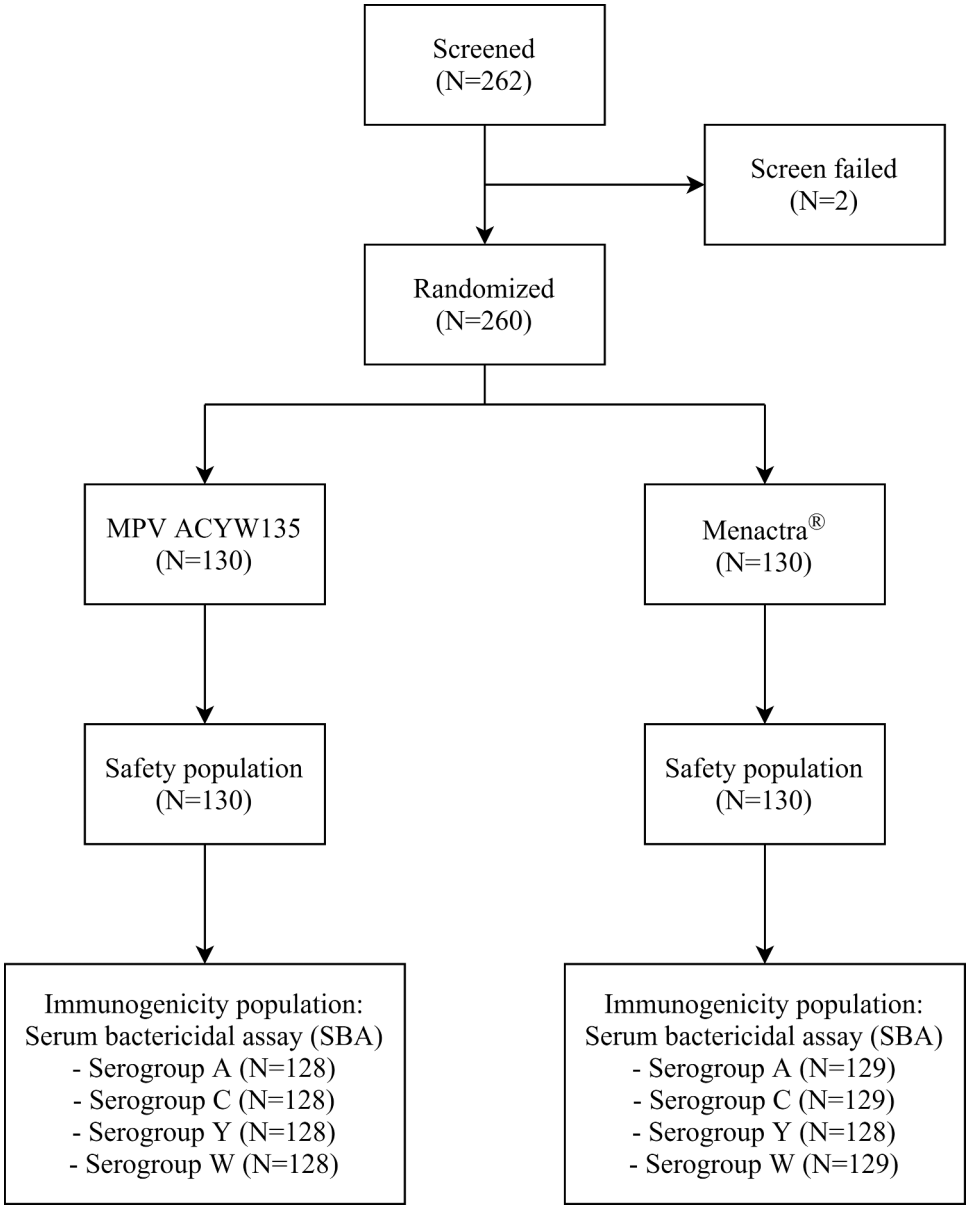

Figure 1. Disposition of study participants.

Table 1. Summary of Demographics at Baseline.

Demographics	All (*N* = 260)	MPV ACYW135 (*N* = 130)	Menactra® (*N* = 130)	*P*
Sex				.7096[a]
Male	125 (48.08%)	64 (49.23%)	61 (46.92%)	
Female	135 (51.92%)	66 (50.77%)	69 (53.08%)	
Age (years)				.1122[b]
Mean (SD)	5.44 (2.37)	5.22 (2.41)	5.67 (2.32)	
Median (q1-q3)	6.00 (3.00–7.00)	5.00 (3.00–7.00)	6.00 (4.00–8.00)	
Min-Max	2, 10	2, 10	2, 10	
Ethnicity				.6214[a]
Bambara	112 (43.08%)	56 (43.08%)	56 (43.08%)	
Fulani	55 (21.15%)	29 (22.31%)	26 (20.00%)	
Sarakole	5 (1.92%)	4 (3.08%)	1 (0.77%)	
Senufo	6 (2.31%)	1 (0.77%)	5 (3.85%)	
Malinke	54 (20.77%)	27 (20.77%)	27 (20.77%)	
Dogon	8 (3.08%)	4 (3.08%)	4 (3.08%)	
Songhai	4 (1.54%)	2 (1.54%)	2 (1.54%)	
Bobo	1 (0.38%)	1 (0.77%)	0 (0.00%)	
Other	15 (5.77%)	6 (4.62%)	9 (6.92%)	
Height (cm)				.1563[b]
Mean (SD)	111.28 (16.96)	109.75 (16.53)	112.80 (17.30)	
Median (q1-q3)	111.50 (98.00–124.50)	110.00 (98.00–123.00)	113.00 (98.00–126.00)	
Min-Max	80, 151	80, 145	80, 151	
Weight (kg)				.2061[b]
Mean (SD)	19.24 (6.38)	18.73 (6.25)	19.74 (6.49)	
Median (q1-q3)	18.40 (14.00–22.60)	17.15 (14.10–22.30)	19.20 (13.90–23.10)	
Min-Max	8.7, 42.5	8.7, 42.5	9.9, 39.7	
Received MenAfriVac® vaccine				-
Yes	260 (100%)	130 (100%)	130 (100%)	
No	0 (0.00%)	0 (0.00%)	0 (0.00%)	

[a]Overall *P* value (2-sided) based on Chi-square test.
[b]Overall *P* value (2-sided) based on Wilcoxon rank sum test.
N: number of subjects included in each group.

study subjects (Table 1), including gender (49.2% males in the MPV ACYW135 group and 46.9% males in the Menactra® group), age [5.2 years (SD±2.4 years) in MPV ACYW135 group and 5.7 years (SD±2.3 years) in the Menactra® group], weight [18.7 kg (SD±6.3 kg) in MPV ACYW135 group and 19.7 kg (SD ±6.5 kg) in the Menactra® group], height [109.8 cm (SD ±16.5 cm) in MPV ACYW135 group and 112.8 cm (SD ±17.3 cm) in the Menactra® group] and vital signs. The most represented ethnic group was Bambara followed by Fulani and Malinké, which were equally distributed between the two vaccine groups. All subjects had received MenAfriVac® vaccine as part of the EPI in Mali which is given as one dose between 9 and 15 months of age.[2]

Immunogenicity

At baseline, no significant difference ($P > .05$) was noted in proportions of subjects with rSBA titers ≥ 128 between the vaccine groups for all serogroups. After vaccination, all subjects (100.0%) had rSBA titers ≥ 128 for serogroup A; 88.3% (95% CI: 81.4% – 93.3%) in the MPV ACYW135 group and 90.7% (95% CI: 84.3% – 95.1%) in the Menactra® group for serogroup C; 98.4% (95% CI: 94.5% – 99.8%) in the MPV ACYW135 group and 99.2% (95% CI: 95.7% – 100.0%) in the Menactra® group for serogroup Y; 89.1% (95% CI: 82.3%-93.9%) in the MPV ACYW135 group and 92.3% (95% CI: 86.2% – 96.2%) in the Menactra® group for serogroup W. Non-inferior

Table 2. Seroconversion rates as defined by proportion of subject with rSBA titers ≥128 at baseline and Day 30 post vaccination in Per-protocol analysis set (PP).

		MPV ACYW135				Menactra®				
Serogroup	Visit	N	n	%	95% CI	N	n	%	95% CI	*P*
A	Baseline	130	129	99.2%	95.8%-100.0%	130	130	100.0%	97.2%-100.0%	1.0000[c]
	Day 30	128[d]	128	100.0%	97.2%-100.0%	129[e]	129	100.0%	97.2%-100.0%	–[a]
C	Baseline	130	1	0.8%	0.0%-4.2%	130	5	3.9%	1.3%-8.8%	.2132[c]
	Day 30	128[d]	113	88.3%	81.4%-93.3%	129[e]	117	90.7%	84.3%-95.1%	.5275[b]
Y	Baseline	130	69	53.1%	44.1%-61.9%	130	74	56.9%	48.0%-65.6%	.5330[b]
	Day 30	128[d]	126	98.4%	94.5%-99.8%	128[ef]	127	99.2%	95.7%-100.0%	1.0000[c]
W	Baseline	130	17	13.1%	7.8%-20.1%	130	23	17.7%	11.6%-25.4%	.3023[b]
	Day 30	128[d]	114	89.1%	82.3%-93.9%	129[e]	119	92.3%	86.2%-96.2%	.3801[b]

N = the total number of subjects included in the Per-protocol analysis set in each group.
n = the number of subjects with rSBA titers ≥ 128 in each group.
% = n/N × 100%.
[a]No *P* value was computed.
[b]Overall *P* value (2-sided) based on Chi-square test.
[c]Overall *P* value (2-sided) based on Fisher's exact test.
[d]Two subjects in the MPV ACYW135 group did not return at Day 30.
[e]One subject in the Menactra® group did not return at Day 30.
[f]One subject in the Menactra® group had no titer obtained at Day 30.

Table 3. Seroconversion rates as defined by proportion of subject with a rSBA ≥ 4-fold increase at Day 30 post vaccination as compared to baseline in per protocol analysis set (PP).

	MPV ACYW135				Menactra®				
Serogroup	N	n	%	95% CI	N	n	%	95% CI	*P*
A	128[b]	67	52.3%	43.3%-61.2%	129[c]	59	45.7%	36.9%-54.7%	.2894
C	128[b]	118	92.2%	86.1%-96.2%	129[c]	121	93.8%	88.2%-97.3%	.6128
Y	128[b]	116	90.6%	84.2%-95.1%	128[cd]	116	90.6%	84.2%-95.1%	1.0000[a]
W	128[b]	114	89.1%	82.3%-93.9%	129[c]	115	89.2%	82.5%-93.9%	.9825

N = the total number of subjects included in the Per-protocol analysis set in each group.
n = the number of subjects with a rSBA ≥ 4-fold increase in each group.
% = n/N × 100%.
[a]Overall *P* value (2-sided) based on Chi-square test.
[b]Two subjects in the MPV ACYW135 group did not return at Day 30.
[c]One subject in the Menactra® group did not return at Day 30.
[d]One subject in the Menactra® group had no titer obtained at Day 30.

immunogenicity of MPV ACYW135 as compared to Menactra® was demonstrated for all serogroups (Table 2).

No significant difference ($P > .05$) was noted in the proportion of subjects with a rSBA ≥ 4-fold increase 30 days after vaccination as compared to baseline unadjusted titers for all serogroups between the two vaccine groups. Non-inferior immunogenicity of MPV ACYW135 as compared to Menactra® was also demonstrated when comparing the percentages of subjects in each vaccine group achieving a rSBA ≥ 4-fold increase after vaccination as compared to baseline unadjusted titers (Table 3). Similar observations were made when comparing the percentages of subjects achieving rSBA ≥ 8 at 30 days after vaccination ($P > .05$) between the two vaccine groups and for all serogroups (Table 4).

GMTs at baseline for serogroup A were significantly higher ($P = .0410$) in the Menactra® group (2,081.0 [95% CI: 1,809.0–2,393.9]) than that in the MPV ACYW135 group (1,611.1 [95% CI: 1,315.1–1,973.7]), while no significant difference was noted at 30 days after vaccination in both GMTs (5,577.2 [95% CI: 4,852.0–6,410.6] in the MPV ACYW135 group and 6,295.7 [95% CI: 5,622.2–7,050.0] in the Menactra® group) and geometric mean fold-increase (GMFI) (3.5 [95% CI: 2.9–4.2]) in MPV ACYW135 group and 3.0 [95% CI: 2.6–3.5]) in Menactra® group) between the two vaccine groups. No significant difference ($P > .05$) was observed in the GMTs for serogroups C, Y and W at baseline between the two vaccine groups as well as at 30 days after vaccination when a significant increase as compared to baseline was observed in both groups and for all serotypes (all $P < .0001$). No significant difference ($P > .05$) was observed in GMFI values for serogroups C, Y and W (Table 5). Reverse Cumulative Distribution Curves of rSBA titers in the two vaccine groups for all serotypes at baseline and 30 days after immunization are shown in Figures 2 and 3.

Reactogenicity

No immediate post-immunization reactions were reported in the study subjects. Solicited local post-immunization reactions between 30 minutes and 7 days after immunization were few. Pain at injection site was reported in a total of five (1.9%) subjects, two (1.5%) in the MPV ACYW135 group and three (2.3%) in the Menactra® group. All pain at injection site were mild, lasted for a maximum of three days and resolved without sequelae. None of the study subjects reported swelling at injection site. The most reported solicited systemic post-immunization reaction was fever; one (0.8%) in the MPV ACYW135 group reported moderate fever and two (1.5%) in the Menactra® group reported mild fever. Other reported systemic post-immunization reactions were loss of appetite in one subject in each of the two vaccine groups and vomiting in one subject in the Menactra® group, all of which were mild, lasted for one day and resolved without sequelae. All solicited local and systemic post-immunization adverse reactions were

Table 4. Proportion of subjects with rSBA titers ≥8 at baseline and at Day 30 post vaccination in per protocol analysis set (PP).

		MPV ACYW135				Menactra®				
Serogroup	Visit	N	n	%	95% CI	N	n	%	95% CI	*P*
A	Baseline	130	129	99.2%	95.8%-100.0%	130	130	100.0%	97.2%-100.0%	1.0000[c]
	Day 30	128[d]	128	100.0%	97.2%-100.0%	129[e]	129	100.0%	97.2%-100.0%	-[a]
C	Baseline	130	6	4.6%	1.7%-9.8%	130	10	7.7%	3.8%-13.7%	.3019[b]
	Day 30	128[d]	118	92.2%	86.1%-96.2%	129[e]	123	95.4%	90.2%-98.3%	.2942[b]
Y	Baseline	130	72	55.4%	46.4%-64.1%	130	76	58.5%	49.5%-67.0%	.6163[b]
	Day 30	128[d]	126	98.4%	94.5%-99.8%	128[ef]	127	99.2%	95.7%-100.0%	1.0000[c]
W	Baseline	130	21	16.2%	10.3%-23.6%	130	25	19.2%	12.9%-27.1%	.5156[b]
	Day 30	128[d]	115	89.8%	83.3%-94.5%	129[e]	119	92.3%	86.2%-96.2%	.4995[b]

N = the total number of subjects included in the Per Protocol analysis set in each group.
n = the number of subjects with rSBA tiers ≥ 8 in each group.
% = n/N × 100%.
[a]No *P* value was computed.
[b]Overall *P* value (2-sided) based on Chi-square test.
[c]Overall *P* value (2-sided) based on Fisher's exact test.
[d]Two subjects in the MPV ACYW135 group did not return at Day 30.
[e]One subject in the Menactra® group did not return at Day 30.
[f]Titer was not measured for 1 subject in the Menactra® group due to insufficient serum aliquot.

Table 5. Comparison of rSBA geometric mean titers between baseline and Day 30 post vaccination in per protocol analysis set (PP).

Serogroup	Study Group	Baseline GMT (95% CI)	Day 30 post Vaccination GMT (95% CI)	Geometric Mean Fold Increase from Baseline (95% CI)	P^a
A	MPV ACYW135	1,611.1 (1,315.1–1,973.7)	5,577.2 (4,852.0–6,410.6)	3.5 (2.9–4.2)	<.0001*
	Menactra®	2,081.0 (1,809.0–2,393.9)	6,295.7 (5,622.2–7,050.0)	3.0 (2.6–3.5)	
	P^b	0.0410	0.1822	0.2662	
C	MPV ACYW135	2.4 (2.1–2.7)	348.6 (247.7–490.5)	148.2 (105.4–208.2)	<.0001*
	Menactra®	2.7 (2.2–3.3)	490.5 (363.1–662.5)	180.5 (128.3–254.0)	
	P^b	0.2144	0.1385	0.4176	
Y	MPV ACYW135	38.4 (23.7–62.1)	2,627.3 (2,033.4–3,394.8)	68.7 (43.4–108.7)	<.0001*
	Menactra®	49.0 (30.2–79.7)	3,008.2 (2,410.7–3,753.8)	58.4 (36.6–93.2)	
	P^b	0.4784	0.4296	0.6241	
W	MPV ACYW135	4.8 (3.3–6.8)	985.9 (630.9–1,540.8)	203.9 (132.6–313.6)	<.0001*
	Menactra®	6.0 (4.0–9.0)	1,459.9 (966.9–2,204.2)	240.0 (150.2–383. 5)	
	P^b	0.3899	0.2021	0.6128	

[a]Paired *t* test was used to calculate *P* values. GMT titer between baseline and Day 30 were compared.
[b]Independent *t* test was used to calculate *P* values. GMT titer between vaccine groups were compared.
**P* value ≤ .05 is considered statistically significant.

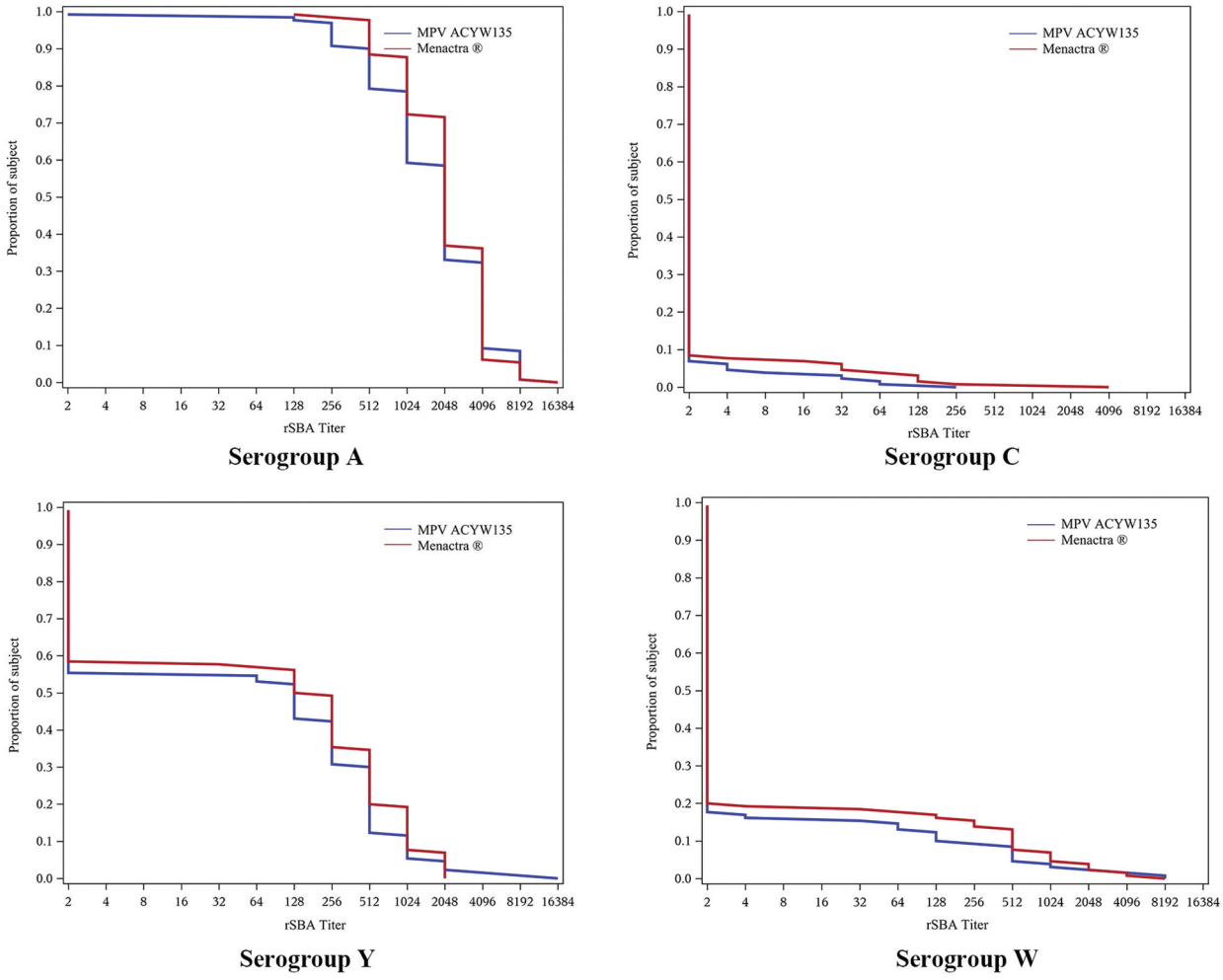

Figure 2. Reverse Cumulative Distribution Curves of baseline rSBA titers - per-protocol analysis set (PP): blue curves stand for MPV ACYW135, and red curves stand forMenactra®.

reported within 4 days after vaccination, none between 4 and 7 days (Table 6).

A total of 27 unsolicited Adverse Events (AEs) were reported in 26 subjects (10.0%) between Day 1 and Day 30 after vaccination, among whom 12 (9.2%) were reported in the MPV ACYW135 group and 14 (10.8%) in the Menactra® group (Table 7). One subject in the Menactra® group reported two unsolicited AEs. None of the unsolicited AEs was reported as being related to study vaccines. The most reported unsolicited AEs were respiratory tract infections such as bronchitisand pharyngitis, which were equally distributed between the two vaccine groups in terms of numerosity, severity and duration. Most unsolicited AEs were moderate in severity, lasted for few days and resolved without sequelae. No SAEs were reported during the study period.

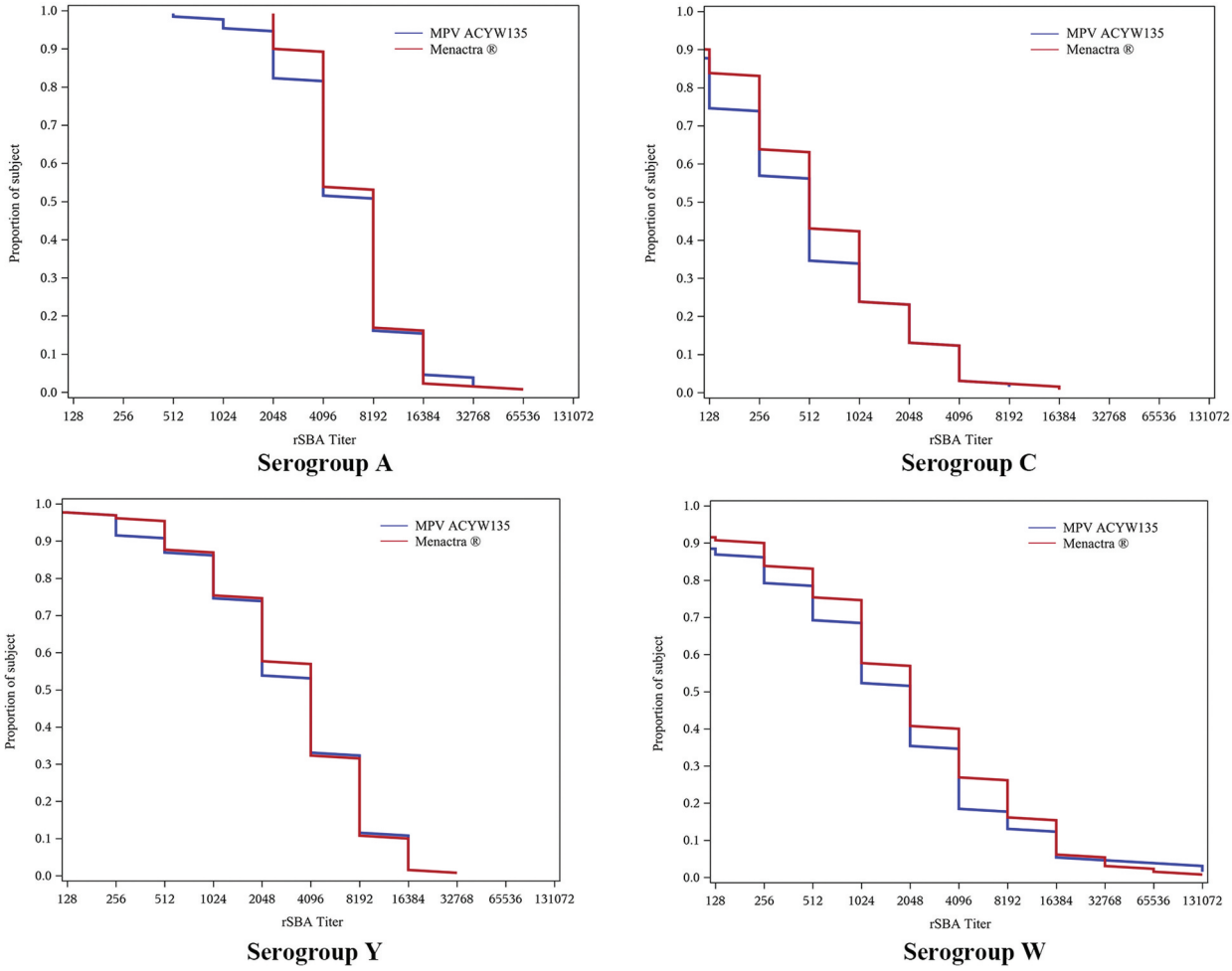

Figure 3. Reverse Cumulative Distribution Curves of rSBA titers 30 Days after Immunization - per-protocol analysis set (PP): blue curves stand for MPV ACYW135, and red curves stand for Menactra®.

Discussion

In this study, Walvax MPV ACYW135 vaccine showed a similar reactogenicity and safety profile to Sanofi Pasteur Menactra®, a licensed and widely used meningococcal conjugate vaccine. The frequency of local and systemic post-immunization reactions and adverse events reported in this study are consistent with other studies performed at the same study site with meningococcal vaccines.[12]

The non-inferior immunogenicity of MPV ACYW135 vaccine as compared to Menactra® vaccine was demonstrated for all serogroups (i.e., A, C, Y, W) using either the criterion of proportion of subjects achieving rSBA titers ≥ 128 and ≥ 8 after vaccination or rSBA ≥ 4-fold increase as compared to baseline GMTs. These are important observations as the rSBA titer ≥ 8 is correlated with protection against meningococcal serogroup C disease[8,9] and a 4-fold increase in GMT is a marker of response to vaccination per existing guidelines on meningococcal vaccines.[11,13]

In both vaccine groups, rSBA titers for serogroup A were high at baseline, which is most likely the result of previous vaccination of the children with MenAfriVac®.[14] In fact, in an earlier study performed in a similar population in the same study area before the introduction of MenAfriVac®, rSBA serogroup A titers were almost 10-fold lower than those found in the present study.[12] However, it appears that the high rSBA baseline titers for serogroup A did not impair the detection of significant increases in GMT after vaccination with respect to baseline titers in both vaccine groups.

The results of this trial are similar to those observed in other trials. In another study performed in Mali in the same study area, the Menactra® vaccine, used as comparator to a meningococcal conjugate pentavalent MenACYWX vaccine, found a similar proportion of subjects with SBA titers ≥ 128 to the four serogroups after vaccination.[15] In a study in Uganda that looked at the immunogenicity of fractional doses of the tetravalent polysaccharide vaccine Menomune® the proportion of subjects vaccinated with the full dose had similar proportion of subjects with SBA ≥ 128 to the four serogroups.[16]

It is acknowledged that polysaccharide meningococcal vaccines provide only direct protection to an individual and are not immunogenic in children below 2 years of age nor are able to induce immunological memory. Finally, they do not prevent the acquisition of carriage and do not provide indirect protection to those unvaccinated.[10,17,18] The development of conjugate meningococcal vaccines has raised the possibility of eliminating meningitis epidemics from Africa. This was demonstrated by the recent

Table 6. Number (%) of subjects with solicited local and systemic reactions within 30 minutes to Day 7 post vaccination by severity.

	MPV ACYW135 (*N* = 130)		Menactra® (*N* = 130)		
	n	%	n	%	*P*
Any Solicited Local Reactions					1.0000[b]
Mild	2	1.5%	3	2.3%	
Moderate	0	0.0%	0	0.0%	
Severe	0	0.0%	0	0.0%	
Pain					1.0000[b]
Mild	2	1.5%	3	2.3%	
Moderate	0	0.0%	0	0.0%	
Severe	0	0.0%	0	0.0%	
Swelling/Induration					-[a]
Mild	0	0.0%	0	0.0%	
Moderate	0	0.0%	0	0.0%	
Severe	0	0.0%	0	0.0%	
Any Solicited Systemic Reactions					.6221[b]
Mild	1	0.8%	4	3.1%	
Moderate	1	0.8%	0	0.0%	
Severe	0	0.0%	0	0.0%	
Fever					.4980[b]
Mild	0	0.0%	2	1.5%	
Moderate	1	0.8%	0	0.0%	
Severe	0	0.0%	0	0.0%	
Irritability					–[a]
Mild	0	0.0%	0	0.0%	
Moderate	0	0.0%	0	0.0%	
Severe	0	0.0%	0	0.0%	
Loss of appetite					1.0000[b]
Mild	1	0.8%	1	0.8%	
Moderate	0	0.0%	0	0.0%	
Severe	0	0.0%	0	0.0%	
Drowsiness					-[a]
Mild	0	0.0%	0	0.0%	
Moderate	0	0.0%	0	0.0%	
Severe	0	0.0%	0	0.0%	
Vomiting					1.0000[b]
Mild	0	0.0%	1	0.8%	
Moderate	0	0.0%	0	0.0%	
Severe	0	0.0%	0	0.0%	

N: number of subjects included in each group.
n: number of subjects who reported corresponding adverse events.
% = n/N × 100%.
[a]No *P* value was computed.
[b]Overall *P* value (2-sided) based on Fisher's exact test.

Table 7. Number (%) of subjects with at least one unsolicited adverse events between Day 0 to Day 30 by severity.

	MPV ACYW135 (*N* = 130)		Menactra® (*N* = 130)	
Severity of Adverse Events	n	%	n	%
Any	12	9.23%	14	10.77%
Mild	2	1.54%	1	0.77%
Moderate	10	7.69%	13	10.00%
Severe	0	0.00%	0	0.00%

Subject ID 1106 in Menactra® group reported 2 AEs, of which one was "RHINITIS" and the other was "ECZEMA" as counted in this table.
N: number of subjects included in each group.
n: number of subjects who reported corresponding adverse events.
% = n/N × 100%.

elimination of meningitis epidemics due to *N. meningitidis* serogroup A by mass vaccination campaigns conducted in several endemic countries of Sub-Saharan Africa using a meningococcal conjugate vaccine against serogroup A (MenAfriVac®).[10,12]

A polyvalent meningococcal ACYWX conjugate vaccine is under development and should become available for use in endemic countries of Sub-Saharan Africa where meningitis outbreaks caused by serogroups W, C and X are still occurring.[15] In fact, severe outbreaks of meningitis with high fatality rates caused by *N. meningitidis* serogroups C and W were reported between 2011 and 2019 in Nigeria, Niger, Togo, and Chad, and with mixed circulation of serogroups X and W in Burkina Faso.[7–9] Reactive immunization campaigns with either conjugate or polysaccharide meningococcal vaccines are recommended by WHO.[7] Recently, it has also been recommended to

stockpile meningococcal vaccines containing serogroup C antigen for preparedness and response to meningitis outbreaks of the same in the sub-Saharan Africa meningitis belt countries.[8,9] Moreover, since the 1980's, meningococcal polysaccharide vaccines have been used by the Chinese National Immunization Programme to control meningitis outbreaks with variable impact on meningitis endemicity.[19,20]

This study demonstrates that MPV ACYW135 vaccine has a similar reactogenicity and immunogenicity profile to Menactra® vaccine. Therefore, MPV ACYW135 vaccine can be stockpiled and used in reactive immunization campaigns to control local outbreaks of *N. meningitidis* serogroups C and W in Africa and in other settings until affordable conjugate polyvalent vaccines become available.[9]

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Disclosure statement

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Authors contribution

SV, JC, SY, LS, SS and ZH designed the study. SOS, MDT, FCH, FT, YT, AT, MK coordinated and implemented the study. SV, RH and LS wrote the first draft manuscript. All the other authors reviewed and contributed to the final version.

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